REMARKS

I. Status of the Claims

Claims 1-74 are pending in the application. Claims 42-53 and 70 are withdrawn as directed to non-elected inventions. Claims 17-22, 24-41, 61, and 66-68 are directed to non-elected species. In the Office Action mailed September 1, 2009, Claims 2 and 3 are rejected under 35 U.S.C. § 112. Claims 1, 6, and 54-60 are rejected under 35 U.S.C. § 102. Claims 1-16, 23, 54-60, 62, 63, and 65 are rejected under 35 U.S.C. § 103. In response, Claims 1-3 have been amended. Claim 4 has been canceled. In view of the amendments and the following remarks, Applicants respectfully request reconsideration and allowance of Claims 1-41, 54-69, and 71-74.

II. The Indefiniteness Rejection of Claims 2 and 3 is Overcome

Claims 2 and 3 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner contends that the phrase "and variant sequences thereof" is not explicitly defined in either the claims or the specification. In response, Claims 2 and 3 have been amended to delete the phrase.

III. The Anticipation Rejection of Claims 1, 6, and 54-60 is Overcome

Claims 1, 6, and 54-60 are rejected under 35 U.S.C. § 102(a) as being anticipated by Madalinski et al., Antibody responses to preS components after immunization of children with low doses of BioHepB, Vaccine 20(1-2):92-97 (2001) (hereinafter "Madalinski"). The Examiner contends that Madalinski teaches that the large surface proteins of HBV (large HBs) comprising preS1, preS2, and S antigens can be used as human vaccines. The Examiner cites other references (Heermann et al., Tam et al., and Roh et al.) for teaching that large HBs contain a T cell epitope in amino acid residues 12-26 of the preS2 region; a B cell epitope in amino acid residues 140-146 of the S region; and a CTL epitope in amino acid residues 179-186 of the

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S region. The Examiner concludes that because the large HBs meet the structural limitations of Claims 1, 6, and 54-60, the subject matter of these claims is anticipated by Madalinski.

Claim 1 has been amended to recite

> An immunogen, characterized in that said immunogen comprises a polypeptide sequence comprising amino acid sequence 1, amino acid sequence 2 and amino acid sequence 3, and these amino acid sequences 1, 2 and 3 are covalently linked together by linking peptides consisting of 3-7 amino acid residues; said amino acid sequence 1 is the sequence of Th cell epitope; said amino acid sequence 2 is the sequence of a CTL epitope from hepatitis B virus; and said amino acid sequence 3 is the sequence of B cell epitope from hepatitis B virus.

Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention. Because Madalinski does not fully disclose the invention as now claimed, the cited reference is not anticipatory.

Madalinski teaches a recombinant vaccine produced via expression of preS1, preS2, and S-protein components. The vaccine is purified from culture media of Chinese hamster ovary (CHO) cells transfected with nucleotide sequences coding for all three surface antigens (preS1, preS2, and S) (Madalinksi, p. 93, Col. 2, first full paragraph). However, Madalinski does not teach or even suggest that the surface antigen peptides are linked together "by linking peptides consisting of 3-7 amino acid residues," as now recited in amended Claim 1.

In view of the amendment to Claim 1 and the above remarks, applicants respectfully submit that the rejection of Claims 1, 6, and 54-60 under 35 U.S.C. § 102(a) is improper because Madalinksi fails to exactly describe the invention as now claimed. Accordingly, applicants request that the rejection under 35 U.S.C. § 102(a) is withdrawn.

IV. The Obviousness Rejection of Claims 1-16, 23, 54-60, 62-65, and 71-74 Is Overcome

Claims 1-16, 23, 54-60, 62, 63, and 65 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,322,789, issued to Vitiello et al. ("Vitiello") and Tam et al., "Vaccine Engineering: Enhancement of Immunogenicity of Synthetic Peptide Vaccines Related

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to Hepatitis in Chemically Defined Models Consisting of T- and B-cell Epitopes," *Proc. Natl. Acad. Sci. U.S.A. 86*:9084-9088, 1989 ("Tam"). Claims 64, 65, 71, and 72 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Vitiello and Tam, and further in view of U.S. Patent No. 6,333,021, issued to Schneider et al. ("Schneider"). Claims 73 and 74 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Heathcoate et al., "A Pilot Study of the CY-1899 T-cell Vaccine in Subjects Chronically Infected With Hepatitis B Virus," *Hepatology 30*(2):531-536, 1999 ("Heathcoate"), in view of Tam.

Applicants respectfully submit that each of the obviousness rejections is improper because, at a minimum, the motivation cited by the Examiner to combine Vitiello and Tam is insufficient to establish a *prima facie* case of obviousness. Applicants therefore disagree with each of the rejections.

A. Claims 1-16, 23, 54-60, 62, 63, and 65 Are Patentable Over Vitiello and Tam

Claims 1-16, 23, 54-60, 62, 63, and 65 are rejected as obvious over Vitiello in view of Tam. The Examiner contends that Vitiello teaches a polypeptide immunogen or a vaccine containing a T helper epitope derived from tetanus toxoid and a CTL epitope derived from HBV. The Examiner admits that Vitiello is silent as to incorporating a B cell epitope into the polypeptide. However, the Examiner asserts that Tam teaches a synthetic peptide vaccine containing T cell and B cell epitopes from HBV. The Examiner concludes that it would be obvious to combine the teachings of Vitiello and Tam to make a polypeptide sequence comprising Th cell, CTL, and B cell epitopes in order to enhance immunogenicity of an HBV vaccine. Regarding an alleged motivation to combine the references, the Examiner asserts that one would have been motivated to generate the claimed invention with a reasonable expectation of success, given that the combination of T helper and CTL epitopes, as well as B cell epitopes,

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can result in increased immunogenicity, as taught an demonstrated by Vitiello and Tam. Applicants respectfully disagree.

KSR Int'l Co. v. Teleflex confirmed that the Graham Factor analysis should be used in determining whether a claimed invention is obvious under 35 U.S.C. § 103(a). 127 S. Ct. at 1727, 1739 (2007). The following subsections set forth (1) the rejected claims; (2) the scope and content of the cited art, and the differences between the rejected claims and the cited art; and (3) an explanation as to why these differences are not rendered obvious by the cited references. In particular, applicants submit that there has been no showing of "an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* at 1741. Each of the rejections is therefore improper.

1. The Rejected Claims

Claim 1, as presently amended, recites

> An immunogen, characterized in that said immunogen comprises a polypeptide sequence comprising amino acid sequence 1, amino acid sequence 2 and amino acid sequence 3, and these amino acid sequences 1, 2 and 3 are covalently linked together by linking peptides consisting of 3-7 amino acid residues; said amino acid sequence 1 is the sequence of Th cell epitope; said amino acid sequence 2 is the sequence of a CTL epitope from hepatitis B virus; and said amino acid sequence 3 is the sequence of B cell epitope from hepatitis B virus.

The remaining claims depend from independent Claim 1. Therefore, applicants' analysis focuses primarily on Claim 1.

2. Scope and Content of the Cited Art and Differences Between the Cited Art and the Rejected Claims

Vitiello teaches a polypeptide containing a T helper cell epitope derived from tetanus toxoid (Vitiello SEQ ID NO: 15) that is identical to the Th cell epitope in elected sequence 1 (SEQ ID NO: 6). The reference also teaches a polypeptide containing a CTL epitope derived from HBV (Vitiello SEQ ID NO: 23) that is identical to the CTL epitope in elected sequence 2

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(SEQ ID NO: 23). The reference discloses that the Th cell peptide can be administered simultaneously or separately with the CTL peptide, but that preferably the Th cell and CTL peptides are linked (Col. 4, lines 13-16). Referring to Example 4, Vitiello teaches that administering an immunizing dose of T helper cell and CTL peptides that are linked together increases specific CTL priming (Col. 25, line 20, through Col. 26, line 16). Vitiello does not teach or suggest incorporating a B cell peptide into a vaccine.

Tam teaches a synthetic vaccine formulated from polypeptides containing the a-determinant of the S protein of HBV surface antigen and residues 12-26 of the preS2 region of the middle protein. Figure 1 shows that residues 14-24 of the preS2 region of the middle protein are identical to elected sequence 3 of the present application (SED ID NO: 48). Tam teaches that **the preS2 peptide determinant serves as a T helper cell epitope** that enhances the immune response of the S region and overcomes the poor immunogenicity encountered with a single epitope of the S region. See Abstract. Tam does not teach or suggest linking an epitope from the preS2 region (e.g., SEQ ID NO: 48 of the present application) to another T helper cell epitope or to a CTL epitope to enhance the immunogenicity of an HBV vaccine.

3. The Differences Between the Cited Art and the Rejected Claims Are Not Obvious Differences

In the context of an obviousness rejection, the Supreme Court explained the importance of "identify[ing] a reason" why a skilled artisan would be prompted to arrive at the presently claimed invention. *KSR*, 127 S. Ct. at 1727. The Court noted that there should be an "explicit" analysis regarding "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* Here, the Examiner's asserted motivation to combine the references does not result in the claimed invention, and at least one cited reference actually teaches away from the claimed invention. Moreover, the Examiner provides no explicit analysis as to why the combination of references would be successful.

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Regarding an alleged motivation to combine the references, the Examiner asserts that one would have been motivated to generate the claimed invention with a reasonable expectation of success, given that the combination of T helper and CTL epitopes, as well as B cell epitopes, can result in increased immunogenicity, as taught and demonstrated by Vitiello and Tam. However, applicants believe that this interpretation of the references is inaccurate. Tam teaches that **the preS2 peptide determinant serves as a T helper cell epitope** to enhance immunogenicity, but not that it serves as a B cell epitope. As such, a skilled artisan would have no motivation to add the preS2 peptide determinant of Tam to the polypeptide of Vitiello because the polypeptide of Vitiello *already contains* a T helper cell epitope. The hypothetical combination of Vitiello with Tam would produce a polypeptide immunogen having *two* T helper cell epitopes and one CTL epitope. Because the polypeptide of Vitiello already contains a T helper cell epitope, it would not be reasonable to expect that adding a second T helper cell epitope (e.g., the preS2 peptide determinant of Tam) would enhance immunogenicity.

In addition, Tam teaches that the a-determinant from the S region is a B cell epitope (p. 9088, Col. 1, lines 4-5). Accordingly, if the preS2 peptide determinant of Tam is considered to be a B cell epitope, as suggested by the Examiner, then the two epitopes disclosed by Tam (e.g., the a-determinant of the S region and the preS2 peptide determinant) would both be considered B cell epitopes. In contrast, the polypeptide immunogen of Vitiello contains a T helper cell epitope and a CTL epitope. Accordingly, there would be no reason to combine the polypeptides of Tam and Vitiello, because neither reference teaches or suggests that B cell epitopes are capable of enhancing immunogenicity of an HBV vaccine.

4. At Least One Reference Teaches Away from the Claimed Invention

As stated above, Vitiello discloses polypeptides containing a T helper cell epitope derived from tetanus toxoid and a CTL epitope derived from HBV. In contrast, Tam teaches away from the use of a T helper cell epitope derived from tetanus toxoid. According to Tam,

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> One function of protein carriers, such as…tetanus toxoid, is often to enhance the immunogenicity of the synthetic peptide…by providing a T helper cell epitope. However, such carriers are not suitable for use in human vaccines. The inclusion of a protein carrier, besides the disadvantage of chemical ambiguity, can lead to the complications of hypersensitivity to the carrier and epitopic suppression.

See p. 9088, Col. 1, first full paragraph. In contrast, the Th cell epitope in elected sequence 1 (SEQ ID NO: 6) is derived from tetanus toxoid. That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness. *See Winner Int'l. Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000). Moreover, there would be no reason to combine the preS2 peptide determinant of Tam with the tetanus-toxoid containing polypeptide of Vitiello because the resulting polypeptide immunogen would "not [be] suitable for use in human vaccines." *Id.*

The foregoing analysis demonstrates that the alleged motivation to combine the references is factually unsupported. Because the alleged motivation to combine the cited references cannot result in the claimed invention and there is no reasonable expectation of success, and further because at least one reference teaches away from the claimed invention, the obviousness rejection is improper and should be withdrawn.

B. The Claimed Invention Demonstrates Greater Than Expected Results and Is Therefore Not Obvious

Before the present application it was difficult to predict that the subject matter of Claim 1 would elicit strong immunity. For example, none of the cited references, whether alone or in combination, teach or suggest that an immunogen comprising a Th cell epitope, a CTM epitope from HBV, and a B cell epitope from HBV covalently linked together by linking peptides consisting of 3-7 amino acid residues would elicit strong immunity.

M.P.E.P. § 716.02(a) states that a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness. Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken

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separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

As evidenced by the Examples 57 through 60, the claimed invention elicited stronger than expected immunity, and is not obvious under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that Claims 1-41, 54-69, and 71-74 are in condition for allowance. Reconsideration of the application and allowance of the pending claims are respectfully requested. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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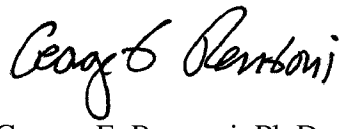

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